DOCKET NO.: 2006_1373A/MRD/01779
Application No.: 10/593,460
Office Action Dated: April 2, 2010

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Peter Herold *et al.*

Confirmation No.: 9975

Application No.: 10/593,460

Group Art Unit: 1626

Filing Date: September 19, 2006

Examiner: Robert H Havlin

For: 5-amino-4-hydroxy-7-(1H-indolmethyl)-8-methylnonamide derivatives as renin inhibitors for the treatment of hypertension

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Robert Mah, hereby declare that:

1) I am a citizen of Canada, residing at Baselstrasse 40L, 4132 Muttenz, Switzerland, and I am a co-inventor of the above identified application.

2) As part of my educational experience, I was a Postdoctoral Research Assistant at Ciba-Geigy AG from 1990-1991; and a Postdoctoral Research Assistant at Stanford University from 1988-1990. I obtained my Ph.D. in Chemistry from Columbia University in1988; and a B.Sc. in Chemistry from the University of Alberta in1982.

3) I have worked in the pharmaceutical field for 19 years. I have extensive lead optimization experience on various cardiovascular projects such as renin inhibitors, nitric oxide donors, aldosterone synthase inhibitors and neutral endopeptidase inhibitors especially when working at Speedel Experimenta Ltd as a scientific expert in medicinal chemistry from 2002 to 2008.

4) My current position is Senior Investigator I at Novartis Pharma AG, where I have been employed for 19 years.

5) It is my understanding that the pending application is directed to 5-amino-4-hydroxy-7-(1H-indolmethyl)-8-methylnonamide derivatives and their use as renin inhibitors for the treatment of hypertension.

6) It is my understanding that claims 1 to 5 and 7 to 10 of the pending application have been rejected because the examiner considers that the specification does not reasonably provide enablement for the asserted utility of the whole of the claim scope. The rejection is based on the fact that Examiner Havlin considers that there is no experimental data in the application to support the claimed utility of the compounds as renin inhibitors.

7) I have personally conducted or been directly responsible for the supervision of the analysis of the structure-activity relationship of several of the compounds described within the pending application.

8) The specific compounds of the invention have been tested according to the test procedures described in *Nussberger et al. J. Cardiovascular Pharmacol., Vol. 9, p. 39-44*, as discussed in the present application on pages 15 to 16. This test detects the action of renin inhibitors by measurement of the reduction of formation of angiotensin I. The test measures the formation of angiotensin I in human plasma. The amount of angiotensin I formed is determined in a subsequent radioimmunoassay. The degree to which the compounds of the invention inhibit the formation of angiotensin I is measured in this system at different concentrations of these compounds. The IC_{50} refers to that concentration of the particular inhibitor which reduces the formation of angiotensin I by 50%.

9) The results of this test carried out for 80 of the specific example compounds of this invention are shown in the Test Report, attached hereto as Exhibit A.

10) Compounds of the invention having a wide range of substituent groups were tested, in order to provide exemplification across the whole scope of the current claims. By way of explanation, with reference to the Test Report, Example 3DD refers to the compound of formula II on page 41 of the present application, where R^1 is example residue "3" from the table starting on page 20 of the application, and NHR^5 is example residue "DD" from the table starting on page 39 of the application. The tests show that compounds of the invention, having a wide range of substituent groups, show inhibitory effects in *in vitro* systems with minimal concentrations of about 10^{-6} to about 10^{-10} mol/l.

11) The experimental data in the Test Report clearly establish the activity of the compounds of the invention.

12) It is my opinion, in view of the technical results, that one of ordinary skill in the art would readily be able to practice the invention across the scope of the claim, based on the information in the application as filed, and additionally in light of the fact that a wide range of the compounds covered by the claims have been shown to have the claimed utility via the attached Test Report.

13) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or by imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

Dated: May 27, 2010

Robert Mah

Robert Mah, Ph.D.

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EXHIBIT A

TEST REPORT

General description

Inhibition of renin in plasma (hPI) are determined by the *in vitro* assay as described in the instant English description on page 15ff. The test used is the one according to Nussberger et. al (1987) *J. Cardiovascular Pharmacol.*, Vol. 9, p. 39-44. The compounds of the present invention show inhibitory effects in in vitro systems with minimal concentrations of about 10^{-6} to about 10^{-10} mol/l.

Example #	hPI IC_{50} (nM)
1K	2.2
3K	3.5
34K	2.6
5K	1.9
3H	23.6
1H	35.0
12K	12.8
2G	19.5
2K	5.9
8K	3.9
13K	10.6
13H	336.0
34B	49.5
5B	30.6
3A	5.4
3B	6.3
3C	4.0
3F	2.1
3G	2.2
5A	12.1
5D	11.5
5G	21.7
5H	13.4
3D	4.1
34A	31.7
34C	32.0
34D	29.5
34G	71.1
34F	24.8
34H	14.8
4A	36.9
4B	30.2
4D	31.0
4G	19.9

Example #	hPI IC_{50} (nM)
4C	20.7
4H	22.0
4k	5.4
7G	7.6
7A	4.1
7B	3.9
7H	10.5
7K	1.5
9A	3.2
9B	3.2
9H	2.7
3DD	5.5
9VV	6.5
9TT	2.9
7VV	5.9
3VV	6.6
7TT	7.0
3TT	5.8
3VV	1.4
7VV	1.4
3Y	14.4
6H	245.0
9VV	1.6
6VV	30.4
17H	13.7
17VV	3.8
29H	242.0
30H	303.0
29VV	12.2
30VV	30.8
5VV	4.8
40H	1.3
40VV	0.8
22H	23.8
40XX	0.6
32VV	5.8
22VV	8.8
23VV	0.7
32XX	4.0
36VV	0.6
36XX	2.1
37XX	1.1
37H	3.7
37K	1.1
37VV	1.2
40K	0.7